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(54) **ANTI-FACTOR XI MONOCLONAL
ANTIBODIES AND METHODS OF USE
THEREOF**

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(58) **Field of Classification Search**
None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

| | | |
|-----------------|--------|------------------|
| 5,877,289 A | 3/1999 | Thorpe et al. |
| 6,989,250 B2 | 1/2006 | Soderlind et al. |
| 8,236,316 B2 | 8/2012 | Gruber et al. |
| 2006/0057140 A1 | 3/2006 | Feuerstein |
| 2015/0099298 A1 | 4/2015 | Wilmen et al. |

FOREIGN PATENT DOCUMENTS

| | | |
|----|----------------|---------|
| WO | WO 2006/055178 | 5/2006 |
| WO | WO 2008/133857 | 11/2008 |
| WO | WO 2009/154461 | 12/2009 |
| WO | WO 2010/065275 | 6/2010 |
| WO | WO 2011/149921 | 12/2011 |
| WO | WO 2011/161099 | 12/2011 |
| WO | WO 2012/004258 | 1/2012 |
| WO | WO 2012/028647 | 3/2012 |
| WO | WO 2012/143510 | 10/2012 |
| WO | WO 2012/152629 | 11/2012 |
| WO | WO 2013/030138 | 3/2013 |

(Continued)

OTHER PUBLICATIONS

Sun et al., J Biol Chem. Nov. 15, 1996;271(46):29023-8.*
Wu et al., J Exp Med. Aug. 1, 1970;132(2):211-50.*
Chothia et al., J Mol Biol. Aug. 20, 1987;196(4):901-17.*
Kunik et al., PLoS Comput Biol. 2012;8(2):e1002388. doi: 10.1371/
journal.pcbi.1002388. Epub Feb. 23, 2012.*
Davie et al., "Waterfall Sequence for Intrinsic Blood Clotting,"
Science 145 : 1310-1312, 1964.
Davie et al., "The Coagulation Cascade: Initiation, Maintenance,
and Regulation," *Biochemistry* 30:10363-10370, 1991.
Fujikawa et al., "Amino Acid Sequence of Human Factor XI, a
Blood Coagulation Factor with Four Tandem Repeats that are
Highly Homologous with Plasma Prekallikrein," *Biochemistry*
25:2417-2424, 1986.

(Continued)

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(57) **ABSTRACT**

Compositions and methods for inhibiting thrombosis with-
out compromising hemostasis are described. Compositions
include anti-factor XI monoclonal antibodies (aXIMabs)
capable of binding to an epitope on the heavy chain of
human FXI, particularly the A3 domain of the heavy chain
of human FXI. Compositions also include epitope-binding
fragments, variants, and derivatives of the monoclonal anti-
bodies, cell lines producing these antibody compositions,
and isolated nucleic acid molecules encoding the amino acid
sequences of the antibodies. The disclosure further includes
pharmaceutical compositions comprising the disclosed anti-
factor XI monoclonal antibodies, or epitope-binding frag-
ments, variants, or derivatives thereof, in a pharmaceutically
acceptable carrier. Methods of the disclosure include admin-
istering the compositions described above to a subject in
need thereof for the purpose of inhibiting thrombosis, reduc-
ing a required dose of an antithrombotic agent in the
treatment of thrombosis, treating metastatic cancer, or treat-
ing an acute inflammatory reaction.

22 Claims, 14 Drawing Sheets